Minu Kesheri
Swarna Kanchan
Travis B. Salisbury
Rajeshwar P Sinha *Editors*

Microbial Omics in Environment and Health

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Editors
Minu Kesheri
Department of Biomedical Sciences Joan C. Edwards School of Medicine, Marshall University
Huntington, WV, USA

Swarna Kanchan
Department of Biomedical Sciences
Joan C. Edwards School of Medicine, Marshall University
Huntington, WV, USA

Travis B. Salisbury
Department of Biomedical Sciences
Joan C. Edwards School of Medicine, Marshall University
Huntington, WV, USA

Rajeshwar P. Sinha
Department of Botany
Banaras Hindu University
Varanasi, Uttar Pradesh, India

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Foreword

I have great pleasure in writing the foreword for the edited book titled ***Microbial Omics in Environment and Health*** by the editors Minu Kesheri, Swarna Kanchan, Travis B. Salisbury and Rajeshwar P. Sinha. I vividly recall the golden days when Prof. Dr. Rajeshwar P. Sinha, as a DAAD fellow awardee, worked under my supervision in my lab as a researcher in Germany. He has a vast scientific experience who has travelled around the globe in the field of academics/research and stands proudly among the top 2% most cited researchers in the world as rightly listed by Stanford University, United States of America. It is a feeling of great ecstasy to witness that Dr. Minu Kesheri is taking this legacy forward in disseminating the knowledge she gained during her doctoral research with Prof. Sinha and her postdoctoral research experience during her international scientific stays in Europe and the United States of America. I am confident that the other two editors, Dr. Swarna Kanchan and Dr. Travis B. Salisbury, have also shown poise in their field of research as evident by their exemplary international scientific research experiences.

Owing to my several decades long experience in academia and research, I am certain that this edited book is an exuberant and comprehensive collection of a wide range of topics reflecting the state of the art and has the potential to revolutionize the understanding and evoke interests of both academicians and researchers. All the chapters in this book are so incorporated that they provide a balanced basic knowledge, discuss recent technologies as well as elaborate various bioinformatics tools to aid in turning data into fruitful scientific insights. Various chapters describe the recent advances in microbial omics on environment and health encompassing microalgal potential, endosymbiosis, crop resilience under changing climatic conditions, crop improvement using epigenomics, cancer, ribosome binding site prediction, gut microbiome, human disease biomarker discovery, public health monitoring, etc. through genomics, metagenomics, transcriptomics, proteomics, metabolomics, integromics, bioinformatics and other omics approaches.

Last but not least, I convey my heartiest congratulations to the contributors from all over the world as authors of various chapters and editors for their hard work. I wish this book a great success!

Friedrich-Alexander University Erlangen-Nürnberg
Bavaria, Germany

Donat-Peter Häder

Preface

Like the omnipresent microbes, in the present scientific era of burgeoning technology, the term 'omics' seems to be an *au courant* catchword in the arena of biological sciences which has the magical power of bestowing ultimate completeness on being suffixed. The origin of this word seems transcendental, being incidentally associated with an ancient Sanskrit word 'Om' that represents the all-powerful 'GOD' encompassing the whole universe. As a word it imparts divine power of unlimitedness and reminds of the biblical verse, 'In the beginning was the Word, and the Word was with GOD, and the Word was GOD' (John 1:1). A geneticist from the Jackson Laboratory, Bar Harbor, ME, USA, named Dr. Thomas H. Roderick gets the credit for christening the very first omics word 'genomics' in 1986, which he initially chose to name a scientific journal now popularly known as *Genomics*. Interestingly about a decade later in 1995, for the first time the term 'proteomics' was coined to represent 'the protein complements of the genome' by Marc Wilkins. This amazing start has led to a journey of dynamically evolving omics terminologies encompassing genomics, transcriptomics, proteomics, metabolomics, lipidomics, interactomics, neuromics, predictomics, integromics and so on.

This edited book represents a sincere effort of comprehensive collection encompassing 15 chapters covering topics reflecting state of the art pertaining to its title, ***Microbial Omics in Environment and Health***. The Chapter 1 describes the interplay of gut microbiome in health and diseases. The Chapter 2 unveils the microbial consequences of environmental degradation on human health through omics approaches. Chapter 3 elaborates microalgal omics approach in understanding human health. Chapter 4 is a panoramic view of microbial multi-species symbiosis. A computational omics protocol for the comparative study of microbiome analysis is discussed in Chap. 5. The role of integromics in tracking the multi-omics expanse in theragnostics is described in detail in Chap. 6. Chapter 7 illustrates various advances in environmental microbiology from a multi-omics perspective. An application of multi-omics in human disease biomarker discovery is the theme of Chap. 8. While Chap. 9 updates us on the status and future strategy in crop improvement using epigenomics, Chap. 11 deals with integrating multi-omics approaches for crop resilience under changing climatic conditions. Chapter 10 focuses on

exploring various secrets of microbes through microbial omics in the environment and health. Chapter 12 provides a detailed description of recent advances in biological omics databases and tools that are used in studying human health. Chapter 13 illustrates peculiar endosymbiosis in the cyanobiont *Nostoc azollae* 0708 using bioinformatics tools. Chapter 14 specifically describes recent advancement in ribosome binding site prediction, ribosome profiling and structural analysis in prokaryotes. Chapter 15 elaborates about microbial metagenomic developments for environmental and public health monitoring.

The book conveys to its readers an avalanche of knowledge encompassing basic concepts and recent advances in technologies about omics and its applications in microbiology, environment and health through illustrative figures and a lucid style. The inclusion of various bioinformatics strategies including relevant codes involved to streamline the research outcomes helps in turning raw data into significant research insights. Therefore, this book shall benefit bibliophiles from the research fraternity, academia, professionals, and experts in the field of life, biomedical, environmental sciences as well as industries related to the development of drug design and novel advances in biotechnological applications. We wish the readers happy reading!

Huntington, WV, USA — Minu Kesheri
Huntington, WV, USA — Swarna Kanchan
Huntington, WV, USA — Travis B. Salisbury
Varanasi, Uttar Pradesh, India — Rajeshwar P. Sinha

Acknowledgments

Editing a book is like preparing a bouquet of colourful floral elements in the form of chapters that are arranged in a way to attract and fulfil the needs of the readers. First and foremost, we would like to pay our sincere gratitude to the Almighty God for everything he has bestowed to us. We wish to convey our sincere thanks to the most reputed scientists and researchers who contributed as authors to facilitate a fruitful accomplishment of this journey. We are grateful to Dr. Brad D. Smith, President, Marshall University, Huntington, WV, USA, whose visionary leadership keeps inspiring for collaborative work and is evident from his quote proclaiming that 'we are each of us angels with only one wing, and we can only fly by embracing one another'. We wish to extend our sincere thanks to Dr. David Gozal, Vice President for health affairs and the Dean of the Joan C. Edwards School of Medicine, Marshall University, for his motivation that keeps our spirits high. It would not be extravagant to thankfully count upon the incessant support for all necessary facilities and exemplary guidance required for fabrication of this book from Dr. Gary O. Rankin, Professor and Chair, Department of Biomedical Sciences and Vice Dean for Basic Sciences, Marshall University, Huntington, WV, USA. We hereby express our hearty thanks to Dr. James Denvir, Professor and Director, Data Science Core Facility, Department of Biomedical Sciences, Marshall University, Huntington, WV, USA, for his consistent encouragement and mentorship. We devote our heartfelt gratitude for encouragement and moral support from Dr. Krista L. Denning, Professor and Chair, Department of Pathology, Marshall University, Huntington, WV, USA. We would like to extend our deep gratitude to Dr. Donald A. Primerano, Emeritus Professor, and former Director of the genomics core at the Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV, USA, for being a constant source of inspiration behind this project. We are glad to express our sincere gratitude and indebtedness to Dr. Donat Peter Häder, Emeritus Professor, and former Director of the Botanical Institute and the Chair of Ecophysiology of Plants at the Friedrich-Alexander University, Erlangen-Nürnberg, Germany. He is also appointed member of the Environmental Effects Panel of the United Nations on the effects of ozone depletion and climate change. It is a boon to have him write the 'Foreword' for our book. We would extend our

heartfelt gratitude for the hard work and support from the publisher's team at Springer Nature, whose guidance, patience, expertise, professionalism, and invaluable commitment are worth many plaudits. Special thanks are due to our panel of reviewers for their assessment, constructive feedback, and insightful comments that aided towards the refinement and structuring of this book. We also wish to offer our indebtedness and gratitude to our family, friends, and mentors for their unwavering support, encouragement, belief, and patience. Last but not least, the cooperation and refreshing motivational smiles from Adarsh Keshari who is the son of Dr. Minu Kesheri and Dr. Swarna Kanchan are worth mentioning and have been the driving force to complete this project in the stipulated time. We thankfully appreciate the research fraternity for their ongoing contribution in advancement of research and wish that this book might fulfil the task of disseminating and enriching the knowledge of our readers and ignite ideas for exploring novel horizons of scientific research for the benefit of mankind.

Contents

Editors and Contributors

About the Editors

Minu Kesheri graduated with a Ph.D. degree from Banaras Hindu University, Varanasi, Uttar Pradesh, India. She was a Postdoctoral Fellow at Boise State University, Boise, Idaho, USA. She had scientific stays at the University of Bordeaux campus in France, Poland, Switzerland, Germany, Spain, Belgium, and India where she delivered invited talks, presented posters, attended workshops, and chaired sessions at conferences. She was former Assistant Professor and Head of Biological and Environmental Sciences Department in India at Shridhar University, Presidency University, and Amity University. She won funding as Principal Investigator and was awarded as young scientist. She is currently working as Research Associate, Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, West Virginia, USA. She has high impact peer-reviewed international publications in the form of research articles, book chapters, and books. She is a reviewer and editorial board member of international scientific journals and committees.

Swarna Kanchan graduated with a Ph.D. degree from Birla Institute of Technology and Science, Pilani, Rajasthan, India. He was a Postdoctoral Fellow at several Institutes/Universities such as the INRIA Bordeaux, France; Nencki Institute of Experimental Biology, Warsaw, Poland, and Boise State University, Boise, Idaho, USA. He worked as an Assistant Professor at the Department of Life Sciences, Presidency University, India. He is currently a Staff Scientist at the Bioinformatics core, Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, West Virginia, USA. He has published several peer-reviewed research articles, book chapters and books with international publishers. He serves as a reviewer and editorial board member for international scientific journals and committees. He has delivered invited lectures, presented posters and attended workshops at national and international institutions in India, France, Germany, Switzerland and the United States of America.

Travis B. Salisbury received a Ph.D. degree from Kent State University, Kent, Ohio, USA. He was a Postdoctoral Fellow at Case Western School of Medicine, USA and Washington State University, USA. He is currently working as an Associate Professor and Director of Genomics Core at the Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, West Virginia, USA. Apart from teaching medical and graduate students, he supervises an active laboratory and has more than a decade of experience in studies on the regulation of gene expression in response to signalling. He won several research grants as a principal investigator from Marshall University, Pharmaceutical Manufacturers Association of America, WV-INBRE next-generation sequencing challenge grant, Cell Differentiation and Development Center grant, Edwards Cancer Foundation, and Edwards Comprehensive Cancer Center (ECCC) grant. He has numerous peer-reviewed international publications and has to his credit various oral and poster presentations at scientific platforms.

Rajeshwar P. Sinha DAAD Fellowship Awardee and Fellow, Society for Applied Biotechnology, India, is a Senior Professor of Molecular Biology, Department of Botany, Banaras Hindu University (BHU), Varanasi, India. He received his Ph.D. in Biotechnology from BHU, Varanasi, India, and visited countries such as Argentina, Austria, Belgium, Canada, China, Germany, Greece, France, Italy, Japan, Luxembourg, Norway, Poland, the Republic of Korea, Spain, Switzerland, the Netherlands, the UK and the USA in the field of academics/research. He is working on Physiological, Biochemical, Molecular, Nanobiotechnological and Computational Biology aspects of cyanobacteria. His primary research focus is on UV-B radiation impacts on DNA damage and repair, Phycobiliproteins, Mycosporine-like amino acids, Scytonemin, etc. He has published over 500 research papers/reviews/book chapters/conference proceedings and edited/authored 12 books. He is a lifetime member of several national and international scientific societies and an editorial board member of various national and international journals. He has over 15460 citations with an h-index of 56 and i10-index of 144. He is among the top 02% most cited scientists in the world.

Contributors

Sanjay Anand Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Anupama Avasthi Amity Institute of Biotechnology, Amity University, Noida, UP, India

Ajay Bhatia CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi, India

Nivedita Chaudhary Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Ashutosh Singh Chauhan Archaeological Survey of India, Agra, Uttar Pradesh, India

Garima Choudhary Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Poornima Dubey Centre of Nanotechnology, Indian Institute of Technology, Roorkee, Uttarakhand, India

Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Wolfgang Gaertner Institute for Analytical Chemistry, University of Leipzig, Leipzig, Germany

Amit Gupta Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Sapana Jha Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Poonam Kaithal Department of Molecular and Cellular Engineering, Jacob Institute of Biotechnology and Bioengineering, SHUATS, Prayagraj, India

Swarna Kanchan Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV, USA

Navkiran Kaur Amity Institute of Biotechnology, Amity University, Noida, UP, India

Garima Kaushik Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Minu Kesheri Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV, USA

Amit Kumar Wayne State University, Detroit, MI, USA

Himansu Kumar National Institute of Animal Science (NIAS), Jeonju, South Korea

Prashant Kumar Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ, USA

Neha Kumari Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Lavanya Amity Institute of Biotechnology, Amity University, Noida, UP, India

Bhagwan Malik Department of Biological Sciences, IISER, Bhopal, Madhya Pradesh, India

Bhagaban Mallik Department of Biological Sciences, IISER, Bhopal, Madhya Pradesh, India

Department of Anatomy and Cell Biology, University of Iowa, Iowa City, IA, USA

Tarun Mishra Department of Biological Sciences, IISER, Bhopal, Madhya Pradesh, India

Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA

Jitendra Narayan CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi, India

Prerna Priya Department of Botany, Purnea Mahila Mahavidyalaya, Purnea University, Purnea, Bihar, India

Palak Rana Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Susanta Roy Department of Life Science and Bioinformatics, Assam University, Diphu, Assam, India

Raj Kumar Sardar Department of Biotechnology, School of Earth Biological and Environmental Sciences, Central University of South Bihar, Gaya, Bihar, India

Shalni Satya Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Shivani Sharda Amity Institute of Biotechnology, Amity University, Noida, UP, India

Sakshi Sharma Department of Environmental Science, School of Earth Sciences, Central University of Rajasthan, Ajmer, Rajasthan, India

Nityendra Shukla CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi, India

Ashish P. Singh Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Satendra Singh Department of Computational Biology and Bioinformatics JSSB, Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad, Uttar Pradesh, India

Smrita Singh Creative Bioinformatics and Science, Morna, Uttar Pradesh, India

Varsha K. Singh Laboratory of Photobiology and Molecular Microbiology, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, India

Rajeshwar P. Sinha Department of Botany, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Shambhavee Srivastav Amity Institute of Biotechnology, Amity University, Noida, UP, India

Swati Srivastava National Institute of Animal Science (NIAS), Jeonju, South Korea

Upasna Srivastava University of California, San Diego, CA, USA

Chapter 1
The Interplay of Gut Microbiome in Health and Diseases

Tarun Mishra, Bhagaban Mallik, Minu Kesheri, and Swarna Kanchan

Abstract The gut microbiome, a complex ecosystem of trillions of microorganisms in the human gastrointestinal tract, has emerged as a central player in maintaining host health and homeostasis. The primary role of the gut microbiome is its involvement in the digestion and absorption of nutrients. It is also responsible for synthesizing essential vitamins and nutrients that the host cannot produce independently. The gut microbiome profoundly impacts the development and maturation of the immune system. Moreover, the intricate communication between gut microbiota and the immune system establishes a symbiotic relationship that profoundly influences systemic immune function. An imbalance in the gut microbial composition contributes to the onset of numerous diseases.

Furthermore, developing techniques like metagenomics, multi-omics, and next-generation sequencing has enabled researchers to study microbial diversity and functional potential, including the gut-brain axis, where the gut microbiome influences cognitive behavior and emotional state through various signaling mechanisms. The use of probiotics, prebiotics, and fecal microbiota transplantation (FMT) to enhance beneficial microbial populations and support gut health is also discussed in this chapter. This chapter provides a comprehensive overview of the indispensable role of the gut microbiome in regulating human health and disease and in influencing various physiological processes beyond traditional digestive function.

T. Mishra (✉)
Department of Biological Sciences, Indian Institute of Science Education and Research Bhopal (IISERB), Bhopal, Madhya Pradesh, India

Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA

B. Mallik
Department of Biological Sciences, Indian Institute of Science Education and Research Bhopal (IISERB), Bhopal, Madhya Pradesh, India

Department of Anatomy and Cell Biology, University of Iowa, Iowa City, IA, USA

M. Kesheri · S. Kanchan
Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV, USA

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Keywords Gut microbiome · Probiotics · Prebiotics · Immunity · Metagenomics · Multi-omics

1.1 Introduction

The microbiome is defined as a community of microorganisms that inhabit a particular environment, especially the collection of organisms living in or on the human body (Berg et al. 2020). The human gut microbiome consists of a vast and diverse collection of microorganisms that inhabit the gastrointestinal tract. This ecosystem consists of bacteria, archaea, viruses, and fungi, collectively known as the gut microbiota (Sprockett and Coyte 2023). Over the past few decades, research in this field has shed light on the profound impact of the gut microbiome on human intestinal homeostasis and disease pathogenesis (Sprockett and Coyte 2023; Fan and Pedersen 2021). The advancement in techniques like next-generation sequencing (NGS) has revealed that the gut microbiome gene pool exceeds 150-fold more than the human genome (Panek et al. 2018).

The gut microbiome is known to regulate various functions in the human body. Bacteria in the gut perform fermentation of food, protection against pathogens, vitamin production, and immune system stimulation. The intestinal microbiota encompasses a rich diversity of over 1500 species, spanning more than 50 distinct phyla. Among these, *Bacteroidetes* and *Firmicutes* predominate, with *Proteobacteria, Fusobacteria, Tenericutes, Actinobacteria*, and *Verrucomicrobia* also contributing to the microbial landscape in humans, constituting up to 90% of the overall microbial population (Laterza et al. 2016). Numerous factors can alter both the composition and functionality of the gut microbiota. These influencing factors encompass host genetics, dietary choices, antibiotic uses, way of living, exercise, and geographical location (Hasan and Yang 2019).

The disruption of the gut microbiota population is associated with a range of human infections, including inflammatory bowel diseases (IBD), obesity, diabetes, allergic conditions, autoimmune disorders, and cardiovascular disease (Akagawa et al. 2021; Calabrese et al. 2020; Wang et al. 2020). Moreover, various strategies exist for modulating the composition and functions of the gut microbiota, such as using probiotics, prebiotics, and techniques like fecal microbiota transplantation (FMT) (Akutko and Stawarski 2021; Ciernikova et al. 2021).

This chapter's objective is to comprehensively explore various roles performed by the gut microbiota and to delve into the influences that shape its microbial composition. Furthermore, we explored the intricate associations between gut microbiota and diseases, delving into numerous therapeutic approaches devised to manipulate and restore equilibrium within the intestinal ecosystem and offering potential treatments for various health conditions.

1.1.1 The Composition of the Gut Microbiome

At the core of the gut microbiome are bacteria, which make up the majority of the microbial population. These bacteria belong to diverse taxonomic groups, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* (Rahman et al. 2021). Each group comprises numerous species and strains with distinct characteristics and functions. The relative abundance of these bacterial groups can vary widely among individuals and is influenced by factors such as diet and lifestyle (Hasan and Yang 2019). Integrative omics approaches have the potential to yield an array of information related to microbiome (Kumari et al. 2018; Srivastava et al. 2024a).

Bacteroidetes and *Firmicutes* are the most abundant bacterial phyla in the gut. *Bacteroidetes* are associated with the degradation of complex carbohydrates and the production of short-chain fatty acids (SCFAs), important energy sources for the host, and play a role in gut health. *Firmicutes*, conversely, are involved in the fermentation of dietary fibers and the production of metabolites that influence host metabolism (Murugesan et al. 2018; Houtman et al. 2022).

In addition to bacteria, the gut microbiome also contains other microorganisms. For example, viruses known as bacteriophages infect and replicate within bacterial cells, potentially impacting bacterial populations and functions. Fungi, such as *Candida* and *Saccharomyces* species, are also part of the gut microbiome and can interact with bacteria in various ways (Perez 2021; Santus et al. 2021). The gut microbiome's composition is not fixed; it can change in response to various factors. Diet is a significant influencer of microbiome composition. A diet rich in fiber and plant-based foods promotes the growth of beneficial bacteria and the production of SCFAs. In contrast, a diet high in processed foods and sugars may lead to the proliferation of less desirable microbes (Zinocker and Lindseth 2018). Metagenomic study unveils the underlying significance of microbial interactions (Kanchan et al. 2020; Kesheri et al. 2024) and aids in visualization of biomarkers (Srivastava et al. 2024b).

The gut microbiome's role in health extends beyond digestion. It interacts closely with the immune system, helping to educate immune cells and maintain a balanced immune response. Dysbiosis, an imbalance in the gut microbial community, has been linked to various health conditions, including inflammatory bowel diseases, obesity, diabetes, and mental health disorders. Host genetics also plays a role in shaping the gut microbiome. Different individuals may have varying levels of susceptibility to certain diseases or conditions due to their genetic makeup, which can impact the types of microbes that thrive in their gut. Research into the gut microbiome is still in its early stages, and scientists are uncovering new insights into its complexity and functions. Advances in DNA sequencing technology have enabled researchers to study the composition and activity of the gut microbiome in greater detail. These techniques have led to identifying specific microbial species and metabolites associated with health or disease states.

1.2 Roles of the Gut Microbiome

The gut microbiome starts to develop before the beginning of life. The gut microbiome plays a significant role in the maintenance of human health. The gut microbiome synthesizes various metabolite products that influence homeostasis upon interaction with the host. The gut microbiome replicates on the surface of the inner lining of the gut and generates a protective lining to prevent any invasion of pathogenic microorganisms (Ali et al. 2020).

1.2.1 Digestion and Nutrient Metabolism

The gut microbiome aids in digesting complex carbohydrates that the host's enzymes cannot break down. The bacteria in the gut produce enzymes that help break down indigestible carbohydrates like lignin, pectin, cellulose, hemicelluloses, oligosaccharides, and polyphenols found in plant-based foods into small molecules that the body can absorb (Thursby and Juge 2017; Lin and Zhang 2017). Nutrimetabolomics serves the purpose for exploring these metabolites (Srivastava et al. 2023; Kanchan et al. 2024). The breakdown of metabolites is assisted mainly by *Bacteroidetes*, *Firmicutes*, and anaerobic gut microorganisms. The small molecules produced escape from the gastrointestinal tract and enter the colon, where it gets absorbed to be used as an energy source (Louis and Flint 2017).

Further, the gut microbiota contributes to the production of vitamins such as biotin, cobalamin, thiamine, riboflavin, pantothenic acid, and nicotine, including vitamins B and K. A group of researchers reported the synthesis of vitamins takes place at different enterotypes: ascorbic acid, riboflavin, pantothenic acid, and biotin are biosynthesized by enterotype 1 (Wu et al. 2011; Arumugam et al. 2011). In contrast, folic acid and thiamine are biosynthesized by enterotype 2. Also, these bacteria break down oligosaccharides and lignin into short-chain fatty acids (SCFAs) like butyric acid, propionic acid, and acetic acids. Short-chain fatty acids (SCFAs), produced by microbial fermentation of dietary fiber, serve as an energy source for intestinal cells and play a role in maintaining gut health. The imbalance in the production of short-chain fatty acids causes the onset of many diseases for the host.

Furthermore, the gut microbiota is known to play a role in the synthesis of bile acids, conjugated fatty acids, and cholesterol. Additionally, the microbial community in the gut contributes to the production of carbohydrates, amines, phenols, branched-chain amino acids, and phenylacetic acid.

Likewise, there are few reports that microorganisms in the gut produce neurochemicals that can affect the functioning of the central and peripheral nervous systems (Holzer 2022). For example, gamma-aminobutyric acid (GABA), a known neurotransmitter inhibitor in brain signaling, is produced by lactic acid bacteria in gut microbiota and modulates gut-brain axis response (Morrison and Preston 2016). Bioinformatic tools and software significantly help in analyzing the big data

obtained from the biological world (Kesheri et al. 2016; Kumari et al. 2016). In silico studies on protein structure modeling have influenced the study of microbial protein-protein interaction and their use in docking studies (Kesheri et al. 2015a; Priya et al. 2017).

1.2.2 Immune System Regulation

The gut microbiome is crucial in educating and regulating the immune system, helping it differentiate between harmful pathogens and beneficial microbes. A well-balanced gut microbiome helps prevent inappropriate immune responses, such as allergies or autoimmune diseases. Antioxidants and other compounds from various natural sources (Ghai et al. 2015, 2016; Mishra et al. 2015a, b; Saxena et al. 2015; Sahu et al. 2023) have been reported to aid in strengthening the immune response and retarding aging (Kesheri et al. 2014, 2017) and may strengthen the proliferation of crucial gut microbiome. The gut microbiome proliferates on the outer lining of the intestinal tract, thereby creating a protective film on the surface. This film of microbes contributes to maintaining the integrity of the intestinal barrier, preventing the entry of the invasion of harmful substances and pathogenic microorganisms from crossing into the bloodstream. Additionally, the production of short-chain fatty acids (SCFAs) by microbiota is used by intestinal epithelial cells as the energy source that strengthens the mucosal barrier. Therefore, the production of SCFAs by microbes has drawn particular attention from researchers because of its role in improving human health and their relevant biotechnological applications (Singh et al. 2017).

Moreover, researchers have discovered the anti-inflammatory and antitumor properties of SCFAs, butyrate, and propionate. It has been shown that people with colon cancer produce less propionate and butyrate than healthy people due to a lack of butyrate-producing microorganisms (Morrison and Preston 2016). Butyrate and propionate show anti-cancerous properties by reducing histone deacetylase activity in colonocytes and immune cells (Bindels et al. 2012; Wei et al. 2016). Several microbial compounds such as mycosporine-like amino acids (Richa et al. 2011a, b) have been screened to possess anti-cancerous properties, and microbial antioxidative enzymes such as superoxide dismutase (Kesheri et al. 2021) and catalase (Kesheri et al. 2022) have been shown to act as the first line of defense against stress (Kesheri et al. 2011, 2015b).

1.2.3 Gut-Brain Axis

The gut-brain axis is a bidirectional communication between the gut and the brain, and the gut microbiome is thought to play a role in this communication (Rhee et al. 2009). The coordination between the gut and brain axis occurs through sympathetic

and parasympathetic systems. The immune and enteric systems are proposed as two extra lines of communication. The gut-brain axis investigation also shows its role in anorexia nervosa (AN) and neurodegenerative dementia like Alzheimer's disease (AD) and neurodegenerative disorders like Parkinson's disease (PD) (Cryan et al. 2020; Dogra et al. 2022; Ghenciulescu et al. 2020).

The coordination between the gut microbiome and brain can influence complex behaviors, stress, anxiety, learning, enteroendocrine signaling, immune activation, enteric reflex, and intestinal permeability. The stability of neurons relies on strength of connection among the neurons mediated by array of pre- and postsynaptic proteins (Mallik et al. 2017, 2022; Raut et al. 2017). However, recent studies have indicated that gut also influences strength of connections among the neurons. Studies using animal models provided pieces of evidence of the gut-brain axis. The *Helicobacter pylori* infection in the gut leads to severe Parkinson's disease (Gorecki et al. 2020). The deposition of amyloid-β in the brain leads to the degeneration of neurons, causing AD. Several factors point toward the role of the gut-brain axis in AD development. The balance of healthy *Bacteroides*/*Firmicutes* is disordered in AD patients, with an increase in abundance of *Bacteroides*, *Gemella*, and *Rikenella* and a reduction in *Clostridioides*, *Bifidobacterium*, *Mogibacterium*, and *Turicibacter* (Liu et al. 2021). Also, the inflammation in the gut lining leads to its permeabilization and leakage of chemicals that cross the blood-brain barrier and damage the central nervous system. One species of *Bacteroidetes*, called *Bacteroides fragilis*, can be directly linked to AD development (Doifode et al. 2021; De la Fuente 2021). The *Bacteroides fragilis* produces a toxin, BFT fragilysin, that has the potential to disrupt the epithelial cell layer of the gastrointestinal tract by degrading a protein called E-cadherin, responsible for synaptic zonula adherens, thus enhancing leakage across the membrane. Additionally, the LPS from *Bacteroides fragilis* is well characterized for inducing inflammation by enhancing pro-inflammatory transcription factor NF-kB (p50)/(p65) complex production. Induction of this complex contributes to neurodegeneration (Cryan et al. 2019).

Further studies and characterization is required to establish the direct link between AD and gut microbiome. The changes in the microbial population with aging lead to the accumulation of bacterial species producing LPS and pro-inflammatory factors, which ultimately leak out, cross brain barriers, and cause neurodegeneration (Mohajeri et al. 2018).

Additionally, gut microbes are involved in converting dietary compounds into bioactive metabolites. For example, they can convert certain dietary polyphenols into bioactive compounds with antioxidant and anti-inflammatory properties, contributing to overall health. Microbes in the gut carry out fermentation processes that produce gases like hydrogen, methane, and carbon dioxide. Certain gut microbes can influence the metabolism and effectiveness of drugs. They can modify drug compounds, impacting how drugs are absorbed, metabolized, and excreted by the body. This can have implications for medication efficacy and potential side effects.

These roles collectively emphasize the importance of a balanced and diverse gut microbiome for maintaining overall health. The gut microbiome's intricate interactions with the host's physiology underscore its potential as a target for therapeutic

interventions and the prevention of various diseases and disorders. Ongoing research continues to unveil the complexities of the gut microbiome and its far-reaching impacts on human health.

1.3 Factors Affecting Gut Microbiome

The composition and diversity of the gut microbiome are influenced by various factors, including genetics, diet, lifestyle, environment, medications, and different health conditions. The interactions between these factors can significantly affect the balance of microbial populations within the gut. Below are some of the key factors that affect the gut microbiome.

1.3.1 Genetics

From previous studies, it is well known that host genetics influences the abundance and richness of microbial taxa and can influence susceptibility to certain diseases and conditions linked to the gut microbiome. The host genes express pattern recognition receptors that sense microorganism in the gut and therefore change the microbes' abundance and microbes' associated disease (Iebba et al. 2016).

One group studied the fecal microbiota from individuals sharing the genetic pool (monozygotic twins) and unrelated individuals. Monozygotic twins, who live in different environments and have diverse food styles, harbor identical microbiota compared to individuals with similar food but distant genetic relatedness (Kurilshikov et al. 2017). Furthermore, research has indicated that specific microorganisms belonging to phyla such as *Actinobacteria*, *Firmicutes*, *Tenericutes*, and *Euryarchaeota* exhibit a higher degree of heritability in comparison to those from the *Bacteroidetes* phylum. These collective observations underscore the significant role that individual genetics play in shaping the composition of the gut microbiota (Chen et al. 2018).

1.3.2 Diet

Diet is one of the most significant factors influencing the gut microbiome. Different dietary components, such as fiber, fats, proteins, and sugars, can selectively promote the growth of specific microbial populations. Diet rich in fiber and plant-based foods tends to support a diverse and beneficial gut microbiome, while diet high in processed foods and sugars can lead to dysbiosis (Hills et al. 2019).

1.3.3 Antibiotics

Antibiotics play a significant role in shaping the gut microbiota, the complex community of microorganisms residing in the gastrointestinal tract. While antibiotics are valuable for treating bacterial infections, their use can have far-reaching effects on the gut microbiota's composition, diversity, and function. These effects can have both short-term and long-term implications for human health (Klingensmith and Coopersmith 2016).

Antibiotics are designed to target and kill or inhibit the growth of specific bacteria. However, antibiotics are not always selective and can impact a broad range of bacteria, including both pathogenic and beneficial species. The use of antibiotics can lead to a temporary reduction in microbial diversity and abundance. The effect of antibiotics on microbiota depends upon the type of antibiotic and the duration of use (Dethlefsen and Relman 2011). For example, intake of clindamycin for 2 years selectively diminishes the *Bacteroides* abundance. Further, treatment of *Helicobacter pylori* infection using clarithromycin reduces *Actinobacteria*, while *Ruminococcus* are decreased using ciprofloxacin and did not recover even after 6 months after treatment (Jakobsson et al. 2010). Another drug called vancomycin treatment increases the abundance of *Proteobacteria* and reduces, *Bacteroidetes*, and *Faecalibacterium* species (Isaac et al. 2017).

When dealing with infections caused by distinct variants of HIV and SARS-CoV-2 (Mishra et al. 2021, 2022b), it is widely recognized that these viruses exploit the host's cellular mechanisms to multiply and reproduce, leading to an increase in interferon levels (Ramdas et al. 2020). These alterations in cytokines and interferon levels also have an impact on the composition of the gut microbiome (Hsieh et al. 2022).

The gut microbiota has a remarkable ability to recover after antibiotic exposure. However, the extent and speed of recovery can vary depending on factors such as the type of antibiotic, duration of use, and individual variability. Consuming probiotics (live beneficial bacteria) and prebiotics (fiber that supports the growth of beneficial bacteria) may help restore a healthy gut microbiota after antibiotic treatment.

1.3.4 Exercise

Exercise has been increasingly recognized as a gut microbiota modulator, significantly affecting its composition and diversity. The relationship between exercise and the gut microbiota is complex and bidirectional, with emerging research suggesting that physical activity can positively impact microbial diversity and overall gut health.

Regular exercise has been associated with greater microbial diversity in the gut. A diverse microbiota is generally considered a sign of a healthy gut. Microbial diversity is linked to improved metabolic health, reduced

inflammation, and a more resilient gut ecosystem. Exercise appears to favor the growth of beneficial gut bacteria, particularly those associated with producing short-chain fatty acids (SCFAs) (Allen et al. 2018). These SCFAs play a role in maintaining gut barrier integrity, reducing inflammation, and supporting overall gut health. Exercise is a key component of weight management and metabolic health. Changes in the gut microbiota induced by exercise might contribute to improved metabolism, reduced fat accumulation, and better insulin sensitivity. Some bacterial taxa like *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* flourish better, while *Proteobacteria* abundance decreases (Rosa et al. 2005). Furthermore, exercise could help treat dysbiosis-associated diseases like obesity and other gut diseases.

1.3.5 Geographic Impacts

The environment in which a person lives can influence their gut microbiome. Climate, altitude, and exposure to certain microorganisms can impact microbial diversity. For example, it was observed that *Firmicutes* improved in nonindustrial areas in adult guts, and Westernized nations showed a higher ratio of *Bacteroidetes* to *Firmicutes* (Gaulke and Sharpton 2018).

1.4 Microbiome and Relation to Diseases

The relationship between gut microbiota and diseases has become a central focus in medical research, as emerging evidence highlights the profound impact of the microbiome on human health. The gut microbiota, comprising a diverse community of microorganisms residing in the gastrointestinal tract, plays a crucial role in various physiological processes. Dysbiosis, an imbalance in the composition and function of the microbiota, has been implicated in numerous diseases.

Researchers have discerned correlations with various pathological states by comparing the microbial population diversity among distinct individuals. Numerous studies have highlighted connections between the presence or absence of diverse microbial species and specific diseases. These investigations not only elucidate associations but also provide a foundation for formulating hypotheses that connect dysbiosis to the origins of various pathological conditions (Fig. 1.1).

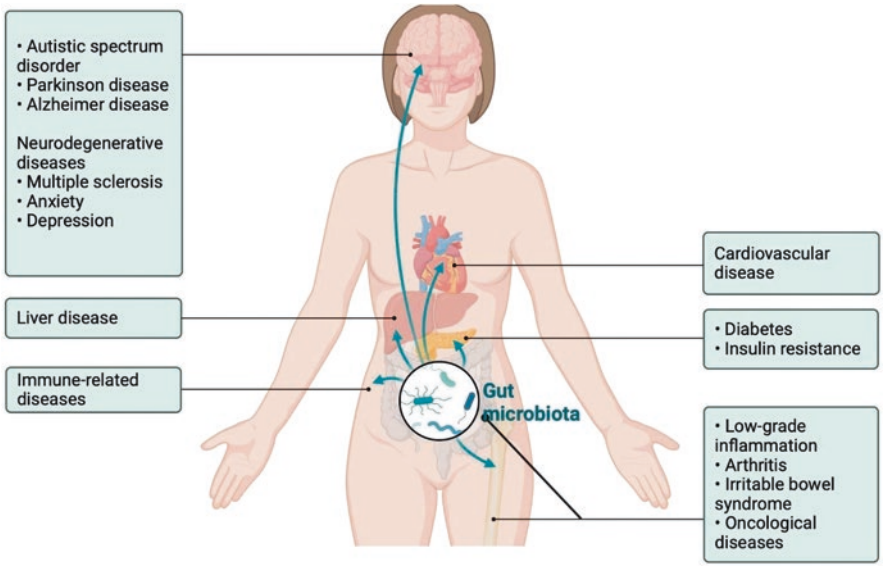

Fig. 1.1 Microbiome dysbiosis contributes to various diseases. (Created by BioRender.com)

1.4.1 Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) encompasses a heterogeneous collection of chronic immune-mediated inflammatory disorders impacting the gastrointestinal system (Lane et al. 2017). The emergence of IBD is attributed to a blend of genetic and environmental factors, including stress, sleep patterns, antibiotic use, hygiene, diet, and smoking. The host genome is speculated to be pivotal in shaping the gut microbiota composition. The two primary forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD) (Schirmer et al. 2018).

CD exerts its influence throughout the entirety of the intestinal tract, presenting with noncontinuous involvement across distinct gut segments. Conversely, UC is confined to the colon and rectum, characterized by continuous prominent bowel inflammation (Kudelka et al. 2016). Extensive research has confirmed a direct correlation between dietary patterns and microbial communities in individuals susceptible to IBD. Conversely, diets rich in vegetables and fruits yield higher levels of short-chain fatty acids (SCFAs), potentially mitigating the risk of CD (Isaac et al. 2017).

IBD patients are presumed to possess a compromised mucus layer within the digestive tract, permitting luminal microflora to infiltrate intraepithelial cells, thereby triggering proliferative and inflammatory processes. Intestinal dysbiosis is a prominent feature linked to IBD, manifesting as a reduction in specific species such as *Bacteroidetes* and *Firmicutes* (Lane et al. 2017). Furthermore, patients with CD and UC exhibit a diminished abundance of *Faecalibacterium prausnitzii* and *Roseburia*. Notably, CD patients demonstrate heightened levels of *Proteobacteria*,

including, *Pasteurellaceae*, *Veillonella parvula*, and *E. coli* (Zhu et al. 2018). Moreover, an upsurge in yeast and fungal taxa has been observed in CD patients, encompassing *Cyberlindnera jadinii*, *Clavispora lusitaniae*, *Candida albicans*, *Saccharomyces cerevisiae*, and *Kluyveromyces marxianus* (Lane et al. 2017).

1.4.2 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is categorized as a functional disorder characterized by various symptoms, including abdominal pain, altered bowel habits, and flatulence. The manifestation of the syndrome symptoms can be attributed to escalated fermentation and gas production. Notably, IBS showcases heightened concentrations of short-chain fatty acids (SCFAs), which, in turn, trigger the release of serotonin from the intestinal mucosa, thereby hastening intestinal transit (Kadooka et al. 2010). Although IBS is not classified as a severe ailment, it does impact approximately 10–15% of individuals, significantly compromising their quality of life (Gupta et al. 2016). This web of gastrointestinal disorders is intricately tied to the interconnection between the gut and the brain, which is called the gut-brain axis (Jeffery et al. 2012).

Conclusive evidence underscores the involvement of the gut microbiota in the pathophysiology of IBS. The qualitative and quantitative shifts within the intestinal microbiota are conspicuous in individuals with IBS. Moreover, microbial dysbiosis within the gut is implicated in the pathogenesis of IBS, as it potentially fosters the adherence of pathogenic microorganisms to the intestinal wall. Extensive studies have corroborated an upsurge in *Firmicutes*, particularly *Clostridium*, *Ruminococcus*, and *Dorea*, along with a decrease in *Ruminococcus albus*, *Bacteroides fragilis*, *B. vulgatus*, and *R. callidus* among IBS patients in comparison to their healthy counterparts (Jeffery et al. 2012; Ghoshal et al. 2012).

1.4.3 Liver Disease

Fatty liver diseases are intricately linked to obesity, alcohol consumption, and metabolic syndrome. Lifestyle, dietary choices, and the intricate role of the gut microbiota influence the onset of this condition. Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat, primarily triglycerides, within hepatocytes. This ailment can progress to more severe stages like liver cirrhosis and hepatocellular carcinoma. While the precise pathogenesis of NAFLD remains elusive, alterations in the gut microbiota are widely acknowledged as a substantial contributor to its development (Betrapally et al. 2016). Several studies indicate reduced levels of *Firmicutes* and *Bacteroides*, alongside notable elevations of *E. coli*, in conjunction with the occurrence of fatty liver diseases.

The pathogenesis of NAFLD might be instigated by several mechanisms. Elevated levels of short-chain fatty acids (SCFAs) and an imbalanced *Bacteroidetes*-to-*Firmicutes* ratio result in enhanced energy extraction, instigating gluconeogenesis and lipogenesis within the liver. Moreover, dysbiosis reduces butyrate production, consequently triggering the activation of lipoprotein lipase and consequent hepatic triglyceride accumulation (Leung et al. 2016).

Ethanol intake might contribute to liver damage by augmenting intestinal permeability and elevating lipopolysaccharide (LPS) levels upon entry. Another mechanism involves the conversion of choline by the gut microbiota into toxic methylamines. The hepatic uptake of these harmful metabolites fuels inflammation. Increased alcohol consumption fosters the proliferation of Gram-negative bacteria, elevating gut permeability and subsequently augmenting the availability of bacterial metabolites and pro-inflammatory molecules like LPS and bacterial toxins to the liver (Pevsner-Fischer et al. 2016).

1.4.4 Diabetes

Type 1 diabetes arises from the destruction of pancreatic β-cells responsible for insulin production, triggered by immune system activity. This form of diabetes typically manifests early in life, coinciding with the formative stage of gut microbial composition, thereby suggesting the pivotal role of these microbes in immune system modulation. Research has illuminated the interplay between the immune system and the gut microbiota, indicating a potential influence on predisposition to type 1 diabetes (Clemente et al. 2012). The gut microbiota in individuals with type 1 diabetes is characterized by heightened levels of *Bacteroidetes*, a deficiency in lactate- and butyrate-producing bacteria, and reduced bacterial functional diversity (Knip and Siljander 2016).

Conversely, type 2 diabetes is a persistent metabolic disorder characterized by insufficient insulin production or impaired glucose metabolism despite insulin presence. This condition is marked by diminished insulin receptor levels or insulin resistance. The composition of the gut microbiota, influenced by both host genotype and lifestyle factors, can consequently impact the risk of developing type 2 diabetes. Individuals with diabetes exhibit elevated proportions of certain phyla, including *Proteobacteria*, *Bacteroidetes*, and *Firmicutes*, compared to their healthy counterparts (Qin et al. 2012).

It is conceivable that lipopolysaccharides derived from the external membranes of Gram-negative bacteria contribute to metabolic endotoxemia by inducing the release of pro-inflammatory cytokines. Multiple studies have revealed that a high-fat diet can modify the composition of the gut microbiota and elevate circulating levels of LPS (Harte et al. 2012).

Furthermore, the gut microbiota exerts influence on polysaccharide and energy metabolism through the production of short-chain fatty acids (SCFAs). Butyrate, in particular, appears to yield beneficial effects on insulin sensitivity by impeding the